

disposable elements for carrying out liquid-liquid micro extraction and liquid-liquid micro extraction. In another aspect the present invention relates to methods for liquid-liquid micro extraction and liquid-liquid-liquid micro extraction, whereby a high enrichment of analyte in an acceptor solution is obtained. In yet another aspect, the invention relates to disposable devices for use in liquid-liquid micro extraction.--

R. Conrad

IN THE CLAIMS:

Please cancel claims 4-10.

Please amend the claims as follows:

1. (Amended) An apparatus for carrying out liquid-liquid micro extraction or liquid-liquid-liquid micro extraction, the apparatus comprising:
caselaw
(a) a first container adapted to receive a sample solution having volume Vs and containing a dissolved analyte;
 - (b) a second container disposed within the first container, the second container having permeable membrane walls, and adapted to receive an acceptor solution having volume Va, wherein:
 - 1) the ratio of Vs to Va is ≥ 50 ; and
 - 2) about $1 \mu\text{l} \leq Va \leq 50 \mu\text{l}$; and
 - (c) a stirring means.
- R.J.D.*

2. (Amended) The apparatus according to claim 1, wherein the second container is a microporous hollow fiber.

3. (Amended) The apparatus according to claim 2, wherein the hollow fiber is formed from a polymer.

11. (Amended) A disposable liquid-liquid micro extraction device comprising a sponge body having defined pore volume, the sponge body adapted for absorption of an acceptor solution.

Please add the following new claims:

12. (New) The apparatus of claim 1, wherein the stirring means is a stirring bar.

13. (New) The apparatus of claim 1, wherein the first container is a disposable container.

14. (New) A method of liquid-liquid micro extraction, the method comprising:

(a) providing an apparatus comprising:

(i) a first container adapted to receive a sample solution having volume Vs and containing a dissolved analyte;

(ii) a second container disposed within the first container, the second container having a permeable membrane wall, and adapted to receive an acceptor solution having volume Va, wherein:

1) the ratio of Vs to Va is ≥ 50 ; and

- 2) about $1 \mu\text{l} \leq V_a \leq 50 \mu\text{l}$; and
- (iii) a stirring means;
- (b) placing the second container in an acceptor solution to form an impregnated second container, wherein the membrane wall of the second container is impregnated with the acceptor solution and the acceptor solution is disposed in the second container;
- (c) placing the impregnated second container in the first container, the first container containing a sample solution containing an analyte;
- (d) stirring the sample solution until extraction equilibrium is established for the analyte in the sample solution and the acceptor solution to form an acceptor solution containing an enriched analyte; and
- (e) removing the acceptor solution containing the enriched analyte from the impregnated second container.
15. (New) A method of liquid-liquid micro extraction, the method comprising:

- (a) providing an apparatus comprising:
- (i) a first container adapted to receive a sample solution having volume V_s and containing a dissolved analyte;

- (ii) a second container disposed within the first container, the second container having a permeable membrane wall, and
adapted to receive an acceptor solution having volume Va,
wherein:
- 1) the ratio of Vs to Va is ≥ 50 ; and
 - 2) about $1 \mu\text{l} \leq Va \leq 50 \mu\text{l}$; and
- (iii) a stirring means;
- (b) impregnating the wall of the second container with a liquid that is immiscible with the sample solution and immiscible with the acceptor solution to form an impregnated second container;
- (c) filling the impregnated second container with a volume of the acceptor solution;
- (d) placing the impregnated second container in the first container, the first container containing the sample solution containing an analyte;
- (e) stirring the sample solution until extraction equilibrium is established between:
- (i) the sample solution and the liquid impregnated in the impregnated second container; and
 - (ii) the liquid impregnated in the impregnated second container and the acceptor solution;
- Qf*

- thereby forming an acceptor solution enriched with analyte; and
- (f) removing the acceptor solution enriched with analyte from the impregnated second container.
16. (New) The method according to claim 14 or 15, wherein the second container is a microporous hollow fiber.
17. (New) The method according to claim 16, wherein the microporous hollow fiber is made of a polymer.
18. (New) The method according to claim 15, wherein both the sample solution and the acceptor solution are aqueous liquids.
19. (New) The method according to claim 15, wherein the liquid impregnated in the impregnated second container is an organic liquid immiscible with aqueous liquids.
20. (New) The method according to claim 15, wherein the sample solution is an alkaline, aqueous biological sample and the acceptor solution is an acidified, aqueous liquid.
- Off record*

REMARKS

I. Status of Claims

Claims 1-11 are pending in the instant application and have been examined. Claims 1-11 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 1-11 also stand rejected under 35 U.S.C. §103(a) as obvious over published PCT patent application WO 97/25606

by Rasmussen et al. ("the Rasmussen et al. reference") in view of U.S. Patent No. 6,164,144 to Berg ("the Berg '144 patent").

Claims 4-10 have been cancelled. Claims 1-3 and 11 have been amended. Claims 12-20 have been added. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version With Markings to Show Changes Made." Reconsideration of the application based on the arguments set forth herein below is respectfully requested.

II. Response to Objection to Specification

The Patent Office states that the application "does not contain an abstract of the disclosure as required by 37 CFR 1.72(b)." Official Action, page 2. As requested by the Examiner, applicants submit herewith an abstract on a separate sheet in compliance with 37 C.F.R. 1.72(b). The abstract is submitted on a separate sheet, numbered page 17, consistent with the page numbering of the application as filed. The abstract is also presented hereinabove and in the Marked-Up Version to Show Changes Made. Support for this amendment is found throughout the application as filed, for example on page 1, lines 3-14. No new matter has been introduced by this purely formal amendment.

Additionally, the Patent Office states that the specification is not organized pursuant to 37 CFR 1.77(b). More particularly, it appears that the Patent Office is requiring section headings to identify the various parts of the

application. Applicants have so amended the specification. The amended specification now contains appropriate section headings in the appropriate order. No new matter has been introduced by this purely formal amendment.

III. Response to the Rejections Under 35 U.S.C. §112, Second Paragraph

Due to the extent of the Patent Office's comments associated with the rejection of claims 1-11 under 35 U.S.C. §112, second paragraph, applicants have organized their response in a claim-by-claim fashion for clarity as follows.

Claim 1

Claim 1 stands rejected under 35 U.S.C. §112, second paragraph, "as vague and indefinite for the recitation of a volume Va because it is unclear if the container has this volume or if the acceptor solution in the container has this volume." Official Action, page 4.

Claim 1 has been amended to clarify that the acceptor solution, and not the second container, has volume Va.

The Patent Office continues, "it is unclear if 'Vs:Va' is a ratio or not, as applicant has not recited it as such." Official Action, page 4.

Although it is submitted that the use of a colon to indicate a ratio is commonplace and the meaning of such notation is well-established in the pertinent field of art, claim 1 has been amended to replace the term "Vs:Va" with the term "the ratio of Vs to Va".

The Patent Office also states, “[a]pplicant should insert ‘An’ at the beginning of the claim. Applicant should also change ‘characterised’ and ‘analysed’ to conform to U.S. spelling. In addition, ‘characterised in’ in line 2 has spaces between the letters, which needs to be fixed.” Official Action, page 4.

Claim 1 has been amended to recite “an” at the beginning of the claim. Claim 1 has also been amended to harmonize the claim language with U.S. spelling.

Continuing with claim 1, the Patent Office rejected this claim “as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections.” Official Action, page 4. “The omitted structural cooperative relationships are the way in which the second container is ‘arranged’ in the first container.” Official Action, page 4.

Claim 1 has been amended to more clearly recite the fact that the second container is disposed within the first container. In this regard, applicants direct attention to Figures 3b and 4b, which depict one embodiment of the recited arrangement in which a second container adapted to receive an acceptor solution is disposed within a first container adapted to receive a sample solution. These figures clearly indicate the configuration of these two containers recited in amended claim 1.

The Patent Office then states “[a] broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.” Official Action, page 4. The Patent Office further states that “claim 1 recites the broad recitation of a first container, and the claim also recites a disposable container, which is the narrower statement of the range/limitation.” Official Action, page 5. The Patent Office additionally states, “claim 1 recites the broad recitation stirring means, and the claim also recites a magnetic bar, which is the narrower statement of the range/limitation.” Official Action, page 5.

The recitation of a disposable container has been removed from the language of claim 1. Additionally, the recitation of a magnetic bar has also been removed from the language of claim 1.

Support for the amendments to claim 1 is found in the claims themselves, as well as throughout the specification, notably on page 11, lines 13-14, page 11, lines 24-26 and 29-30, page 11, lines 23-24 and in the Drawings, notably Figures 3b and 4b. No new matter is introduced by the amendments to claim 1.

Claim 2

In its rejection of claim 2 under 35 U.S.C. §112, second paragraph, the Patent Office states, “Applicant should insert ‘The’ at the beginning of the claim.

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In addition, applicant should remove the spaces between the letters of 'characterised in', while also changing 'characterised' and 'fibre' to conform to US spelling." Official Action, page 5.

Claim 2 has been amended to recite "The" at the beginning of the claim. Additionally, claim 2 has been amended to harmonize the claim language with U.S. spelling.

The Patent Office then states, "applicant should insert 'claim' before the number 1 in the first line of the claim." Official Action, page 6.

Claim 2 has been amended to recite "claim" before "1".

Support for the amendments to claim 2 is found in the claims themselves, since the amendments to claim 2 are purely formal in nature. No new matter is introduced by the amendments to claim 2.

Claim 3

The Patent Office has rejected claim 3 as "being in improper form because a multiple dependent claim should refer to other claims in the alternative only." Official Action, page 6.

Claim 3 has been amended to refer only to claim 2, thereby removing the multiple dependent claim language identified by the Patent Office.

Next, the Patent Office has rejected claim 3 "as vague and indefinite for the recitation of 'the container'. Since there are multiple containers, it is unclear to which container application is referring." Official Action, page 6.

Claim 3 has been amended to remove reference to a container.

Additionally, the Patent Office states "the intended meaning of the term 'active polymer' is unclear, thereby also rendering the claim vague and indefinite." Official Action, page 6.

Claim 3 has been amended to clarify that, in one embodiment, a hollow fiber can be made of a polymer.

Again, the amendments to claim 3 are purely formal in nature and, thus, support for these amendments is found in the claims themselves. Additional support can be found in the specification on page 9, lines 1-2, on page 10, lines 4-5, and on page 10, lines 31-32. No new matter is introduced by the amendments to claim 3.

Claim 4

With respect to claim 4, the Patent Office states the claim "recites the limitation 'the use' in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim." Official Action, page 6. The Patent Office then states "applicant should remove the spaces between the letters of 'characterised in', while also changing 'characterised' to conform to US spelling. Official Action, page 6. The Patent Office continues, "the recitation of 'the membrane wall is impregnated' is vague and indefinite because claim 1, on which claim 4 depends, refers to multiple walls, so it is unclear to which wall applicant is referring." Official Action, page 6. Finally, the Patent Office states

"the term 'enriched analyte' in step d renders the claim vague and indefinite because applicant has not recited anywhere in the process how the analyte becomes enriched." Official Action, page 6.

Claim 4 has been cancelled, rendering the rejection of this claim moot.

Claim 5

The Patent Office states claim 5 "recites the limitation 'the use' in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim." Official Action, page 6. The Patent Office continues, "applicant should remove the spaces between the letters of 'characterised in', while also changing 'characterised', 'immobilisation', and 'immobilised' to conform to US spelling." Official Action, page 6. The Patent Office then states the "term 'thereof' in step b is vague and indefinite because it is unclear, with the present terminology, what the container is filled with." Official Action, page 6. The Patent Office states "the recitation of 'immobilised liquid' is vague and indefinite because there is no positive recitation of a step in which liquid is immobilized. The phrase 'for immobilisation' is only an intended use and does not satisfy this requirement." Official Action, page 7. Finally, the Patent Office states "the term 'enriched analyte' in step d renders the claim vague and indefinite because applicant has not recited anywhere in the process how the analyte becomes enriched." Official Action, page 7.

Claim 5 has been cancelled, rendering the rejection of this claim moot.

Claim 6

Initially, the Patent Office states “[I]n claims 6-10, applicant should replace ‘A’ at the beginning of the claim with ‘The.’” Official Action, page 7.

Claims 6-10 have been amended to recite “The” at the beginning of the claims.

The Patent Office then rejects claim 6 “as being in improper form because a multiple dependent claim should refer to other claims in the alternative only.” Official Action, page 7.

Further, the Patent Office states “applicant should remove the spaces between the letters of “characterized in”, while also changing ‘characterised’ and ‘fibre’ to conform to US spelling.” Official Action, page 7.

Claim 6 has been cancelled, rendering the rejection of this claim moot.

Claim 7

In its rejection of claim 7, the Patent Office states “applicant should remove the spaces between the letters of ‘characterised in’, while also changing ‘characterised and ‘fibre’ to conform to US spelling.” Official Action, page 7.

The Patent Office further states “the intended meaning of the term ‘active polymer’ is unclear, thereby also rendering the claim vague and indefinite.” Official Action, page 7.

Claim 7 has been cancelled, rendering the rejection of this claim moot.

Claim 8

The Patent Office rejected claim 8 "as being in improper form because a multiple dependent claim should refer to other claims in the alternative only."

Official Action, page 7.

The Patent Office also states "applicant should remove the spaces between the letters of 'charaterised in', while also changing 'characterised' to conform to US spelling." Official Action, page 7.

Claim 8 has been cancelled, rendering the rejection of this claim moot.

Claim 9

The Patent Office rejected claim 9 "as being in improper form because a multiple dependent claim should refer to other claims in the alternative only."

Official Action, page 7.

Continuing, the Patent Office states "applicant should remove the spaces between the letters of 'characterised in', while also changing 'characterised' and 'immobilised' to conform to US spelling." Official Action, page 8.

The Patent Office also rejected claim 9 "as vague and indefinite for the recitation of 'liquid immobilized in the membrane' because there is no positive recitation of this step in this claim or on any claim on which claim 9 depends."

Official Action, page 8.

Claim 9 has been cancelled, rendering the rejection of this claim moot.

Claim 10

The Patent Office rejected claim 10 "as being in improper form because a multiple dependent claim should refer to other claims in the alternative only." Official Action, page 8.

Next, the Patent Office states "applicant should remove the spaces between the letters of 'characterised in', while also changing 'characterised' to conform to US spelling." Official Action, page 8.

Finally, it is the Patent Office's position that "the two recitations of 'basic' render the claim vague and indefinite because it is unclear if applicant is referring to pH or not. Applicant may wish to consider using the term 'alkaline'." Official Action, page 8.

Claim 10 has been cancelled, rendering the rejection of this claim moot.

Claim 11

The Patent Office has rejected claim 11, stating "[c]laim 11 recites the limitation 'the form' in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim." Official Action, page 8.

The term "the form" has been removed from the claim.

The Patent Office also states "applicant should remove the spaces between the letters of 'characterised in', while also changing 'characterised' and 'immobilised' to conform to US spelling. Official Action, page 8.

Claim 11 has been amended to harmonize the claim language with U.S. spelling.

Further, it is the Patent Office's position that "the recitation of having the form of a sponge is vague and indefinite because a sponge will take the form of the container into which it is inserted." Official Action, page 8.

The term "the form" has been removed from the claim.

Support for the amendments to claim 11 is found in the claims themselves, since the amendments to claim 11 are purely formal in nature. No new matter is introduced by the amendments to claim 11.

IV. Response to the Rejections Under 35 U.S.C. §103(a)

The Patent Office has rejected claims 12-23 under 35 U.S.C. §103(a) based on the Rasmussen et al. reference in view of the Berg '144 Patent. The Patent Office's basis for this rejection is set forth in detail at pages 9-11 of the Official Action. Applicants respectfully traverse the rejection and submit the following comments.

The Patent Office's Rejection of Claims 1-11

The Patent Office characterizes the Rasmussen et al. reference as disclosing "a device and method from liquid-liquid microextraction. The method comprises proving [sic] a carrier, modifying the carrier, immobilizing a solvent (acceptor solution) on the carrier surface, contacting the carrier with the sample

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(which may be in solution), concentrating and fixing the analyte of interest to the solvent, and analyzing the carrier." Official Action, page 9.

The Patent Office continues with its characterization of the Rasmussen et al. reference: "Preferably, a carrier is used as the fiber. The fibers for use with the invention may be made of porous polymers such as polyacrylate. The amount of solvent to be immobilized on the solvent is in the range of 1-5 ul (page 4)." Official Action, page 9.

The Patent Office then discusses its interpretation of a method allegedly disclosed in the Rasmussen et al. reference:

The carrier with immobilized solvent is inserted into the sample solution, where the pH may be altered to favor partitioning of analyte and solvent (page 5). In one embodiment, the fiber is withdrawn into the needle of a syringe, and the needle is used to penetrate the septum of a solvent vial, at which time the fiber is lowered and solvent is immobilized. The fiber is then withdrawn back into the needle and used to penetrate the sample vial. After the fiber is lowered into the vial, analytes are partitioned by agitating the vial (page 7).

Official Action, page 10.

The Patent Office notes that the Rasmussen et al. reference "does not specifically teach the use of a hollow fiber, magnetic stirring bar, and acidified acceptor solution, or a sponge." Official Action, page 10.

The Patent Office characterizes the secondary reference, the Berg '144 patent, as disclosing "methods and device for solid phase microextraction (SPME). The reference discloses the use of a fiber with SPME, wherein the

fiber acts as a 'sponge'. In addition, the reference also teaches the use of a magnetic stirring bar as the means of agitation of a sample in a vial." Official Action, page 10.

Summarily, it is the Patent Office's position "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use a magnetic stirring bar, a hollow fiber, and an acidified acceptor solution with the invention of Rasmussen et al." Official Action, page 10.

The Patent Office reasons "[b]y using a hollow fiber, one would have been able to fill the fiber with acceptor solution rather than immobilizing the solution of the surface of the fiber. With such an arrangement, partitioning will occur between analyte and acceptor within the fiber, at which time acceptor solution with analyte can be removed and analyzed." Official Action, page 10.

Continuing, the Patent Office contends, "[l]t would have further been obvious to use a magnetic bar as the stirring means to establish extraction equilibrium (partitioning between sample and acceptor) for the analyte because magnetic stir[r]ing bars are very well known in the art for use when agitation is necessary, as taught by Berg et al." Official Action, pages 10-11.

It is the Patent Office's further opinion that "it would have been obvious to acidify the acceptor solution of Rasmussen et al. because Diazepam, the analyte of interest in Example 1, has its highest partition coefficient at an acidic pH. Finally, it would have also been obvious to modify the method and device

of Rasmussen et al. by using a sponge instead of a fiber as the disposable container." Official Action, page 11.

Applicants' Arguments

Applicants initially note that claims 4-10 have been cancelled, but correspond to new claims 14-20. Therefore, the following remarks are directed not only to original claims 1-3 and 11, but to new claims 12-20 as well. Thus, in the remarks below, when the term "claims 1-11" is recited, it is intended that the remarks are also applied to claims 12-20.

The Patent Office notes that the primary reference, the Rasmussen et al. reference, does not teach the use of a hollow fiber, a magnetic stirring bar, an acidified acceptor solution or a sponge (Official Action, page 10) and particularly not in an LLME or LLLME method. The Berg '144 patent does not supplement the omissions from the primary reference. In view of at least the deficiencies in the primary reference identified by the Patent Office and the omissions of the Berg '144 patent, applicants respectfully submit, the Patent Office has not presented a link between these references and the pending claims and has instead attempted to piece together references in an attempt to reconstruct the claimed invention by impermissible hindsight reasoning. ("As in all determinations under 35 U.S.C. section 103, the decision-maker must bring judgment to bear. It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a

template and selecting elements from references to fill the gaps." In re Gorman, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991) (citation omitted).)

Applicants respectfully submit that in its rejection of claims 1-11 of the present invention under 35 U.S.C. §103(a), the Patent Office has employed impermissible hindsight analysis. Applicants therefore submit that in view of the Patent Office's hindsight reconstruction of the invention, claims 1-11 are not obvious in view of the cited references and request that of the rejection of claims 1-11 under 35 U.S.C. §103(a) be withdrawn.

Even if it is assumed, for argument's sake, that the Patent Office has not employed impermissible hindsight reasoning, applicants submit that the Patent Office still has not presented a prima facie case of obviousness. A prima facie case of obviousness requires that each prong of a three prong test be met. Specifically, the cited references, alone or in combination, must disclose each and every element of the claimed invention, the references must supply a suggestion or motivation to combine the references to arrive at the claimed invention and there must be a reasonable likelihood that one of ordinary skill in the art can successfully make the suggested combination.

By the Patent Office's own admission, the Rasmussen et al. reference, the Patent Office's primary reference, fails to disclose at least the use of a hollow fiber, a magnetic stirring bar, an acidified acceptor solution or a sponge in the context of a liquid-liquid microextraction or a liquid-liquid-liquid

microextraction. This deficiency is not compensated for by the other reference cited by the Patent Office, the Berg '144 patent.

Even if the Berg '144 patent could somehow be construed to disclose the use of a fiber as a sponge in an SPME separation as the Patent Office contends, neither the Berg '144 patent nor the Rasmussen et al. reference discloses the use of a hollow fiber or an acidified acceptor solution in a liquid-liquid microextraction or a liquid-liquid-liquid microextraction, which are *combinations* *of* *elements*, embodiments of the subject patent application. At least these aspects of the present invention, which are embodied in the claims of the subject patent application, are absent from the cited references and no combination of the cited references can be made that discloses these elements.

For example, the Patent Office states "it would have been obvious to acidify the acceptor solution of Rasmussen et al. because Diazepam, the analyte of interest in Example 1, has its highest partition coefficient at an acidic pH." Official Action, page 11. The only claim of the subject patent application that recites an alkaline sample solution and an acidic acceptor solution is claim 11, which depends from new claim 15. Applicants submit that claim 15 is patentable, and thus claim 11, which incorporates the elements of claim 15, is also patentable.

on what basis

More particularly, applicants submit that, even if the Rasmussen et al. reference does disclose the observation that Diazepam has its highest partition coefficient at an acidic pH as the Patent Office asserts, the Rasmussen et al.

reference, the sole reference cited by the Patent Office in this step of its obviousness analysis, does not disclose numerous other aspects of the claimed invention and therefore does not render any of claims 1-11 obvious. For example, the Rasmussen et al. reference does not disclose an apparatus comprising first and second containers, wherein the second container comprises permeable membrane walls, and is adapted to receive an acceptor solution having volume V_a , wherein: (1) the ratio of V_s to V_a is ≥ 50 ; and (2) about $1 \mu\text{l} \leq V_a \leq 50 \mu\text{l}$. Thus, even assuming the Patent Office's characterization of the Rasmussen et al. reference is accurate, this single reference does not disclose each and every element of the present invention and thus does not render any claim of the subject application obvious in view of the Rasmussen et al. reference, including claim 11.

Summarily, the cited references cannot be combined to disclose each and every limitation of the claimed invention. Notably, the cited references do not disclose the use of a hollow fiber, a magnetic stirring bar, an acidified acceptor solution or a sponge, among other elements in an LLME or LLLME method. Thus, the combination of references cited by the Patent Office fails the first prong of a prima facie case of obviousness.

Even assuming arguendo that the combination of the cited references does disclose each and every element of the claimed invention, applicants submit that the cited references offer no explicit or implicit suggestion to

combine the cited references as proposed by the Patent Office. Therefore, the second prong of a prima facie case of obviousness is not met. *not being provided*

More particularly, applicants note the Patent Office's contention that "[b]y using a hollow fiber, one would have been able to fill the fiber with acceptor solution rather than immobilizing the solution on the surface of the fiber." Official Action, page 10. Applicants submit, however, that in the arrangement of the Rasmussen et al. reference, in which the solution is immobilized on the surface of a carrier, an additional step of desorbing the analyte from the surface of the carrier is required. While the method of the Rasmussen et al. reference might be effective, it requires this additional desorbing step. The apparatus of the present invention, on the other hand, employs a solution disposed in a container (in one embodiment, a hollow fiber), and represents the first time that a porous container (e.g., a hollow fiber) was employed in a static micro extraction device suitable for extraction of analytes with high enrichment from biological samples through a liquid membrane into an aqueous or organic acceptor solution. No such desorbing step is required in the present invention, *also not required in combination* since the analyte is concentrated in the acceptor solution and not on the walls of the container. This also offers the advantage that an analyte-enriched acceptor solution can be injected directly into an analytical instrument, such as a gas chromatograph, a mass spectrometer. This advantage is not disclosed in *any* the Rasmussen et al. reference, which presents a different solution to the problem of extraction and concentration of an analyte. In view of the above,

more
more
advantages

applicants submit that one of ordinary skill in the art would not be motivated, particularly in view of the lack of an implicit or explicit suggestion in the Rasmussen et al. reference, to make the modification suggested by the Patent Office. The lack of such motivation is particularly glaring in view of the fact that the modification propounded by the Patent Office would require an additional step in an extraction method, namely desorption of the analyte from the carrier.

Next, the Patent Office contends "it would have been obvious to use a magnetic bar as the stirring means to establish extraction equilibrium . . . as taught by Berg et al." Official Action, pages 10-11. Although the use of a stirring bar might be disclosed in the Berg '144 patent, this reference discloses an entirely different approach to extraction, namely an SPME-based approach. The Patent Office notes that "both Berg and Rasmussen et al, are drawn to extraction methods" (Official Action, page 11), however the extraction methods, and thus the associated apparatuses, of these references are very different from that of the present invention. Applicants submit that the disparity between the SPME approach of the Berg '144 patent and the extraction methods and apparatuses of the present invention would not motivate one of ordinary skill in the art to consider the disclosure of the Berg '144 patent in an evaluation of the present invention, particularly in view of the lack of an implicit or explicit suggestion to do so.

Continuing, the Patent Office argues "it would have been obvious to modify the method and device of Rasmussen et al. by using a sponge instead

of a fiber as the disposable container. Since Berg teaches that the fiber of the method acts as a sponge, one would have had a reasonable expectation of success in carrying out the method of Rasmussen et al. with the replacement of the fiber with a sponge material." Official Action, page 11. However, applicants again respectfully submit that the approaches of the Rasmussen et al. reference and the Berg '144 patent are distinct from that of the present invention.

More particularly, the Berg '144 patent is focused on SPME, which is entirely different from the LLME and LLLME methods and apparatuses of the present invention, and therefore an analogy between these two approaches fails. As noted in the specification of the subject patent application, "When SPME is applied to bioanalytical samples such as plasma or urine several difficulties are observed. In drug analysis enrichment from a biological matrix is greatly reduced as compared to enrichment from a pure water sample. In addition the polymeric acceptor phase is easily contaminated . . . and cross contamination between samples may easily occur." Specification, page 3, lines 19-25. See also, the Rasmussen et al. reference, page 3, lines 17-32.

*only related or
containing
features*

Applicants thus submit that contrary to the Patent Office's contention, one of ordinary skill in the art, recognizing the limitations of the SPME method of the Berg '144 patent and the lack of any implicit or explicit suggestion in either of the cited references, would not be motivated to modify the apparatus of the Rasmussen et al. reference to incorporate a sponge as a carrier. In fact,

the cited Rasmussen et al. reference highlights some of the reasons one of ordinary skill in the art would not be motivated to make the combination suggested by the Patent Office.

As the C.A.F.C. stated, “[i]t is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor.” Northern Telecom Inc. v. Datapoint Corp., 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990) (citations omitted). Applicants submit that no such suggestion is presented in the cited references and that, at best, the cited references are simply an “invitation to experiment” and present an “obvious-to-try” situation.

An “obvious to try” situation is held to exist:

when a general disclosure may pique the scientist’s curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

In re Eli Lilly & Co., 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990). Courts have painstakingly distinguished between obviousness under 35 U.S.C. §103 and an “obvious-to-try” situation. “[W]e have consistently held that ‘obvious-to-try’ is not to be equated with obviousness under 35 U.S.C. §103.” The Gillette Co. v. S.C. Johnson & Son Inc., 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990). Applicants submit, therefore, that the cited references alone or in combination

present at best an "obvious-to-try" situation and lack both a suggestion and the motivation to modify the references to arrive at the present invention.

Since no suggestion or motivation to combine the cited references to arrive at the claimed invention exists in the cited references -- indeed no such combination is even possible -- the third prong of the prima facie case, namely the likelihood of success in making the proposed combination, is moot.

Applicants respectfully submit that it is not possible for the references cited by the Patent Office to be combined so as to arrive at the invention recited in claims 1-11, or new claims 12-15, of the present invention. Additionally, there is no disclosure in any of the references suggesting such a combination. Moreover, since the references do not disclose the combination, the cited references offer no motivation to make the claimed combination. As the C.A.F.C. has long held, "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." Carella v. Starlight Archery and Pro Line Co., 231 U.S.P.Q. 644 (Fed. Cir. 1986) (citation omitted). No such teaching, suggestion or incentive appears in the cited references.

Applicants respectfully submit that the Patent Office has not presented a prima facie case of obviousness. As such, applicants request that rejection of claims 1-3 and 11 under 35 U.S.C. §103 be withdrawn. Applicants further

submit that claims 1-3 and 11 and new claims 12-20 are in condition for allowance and respectfully solicit the same.

V. New Claims 12-20

Claims 12 to 20 have been added. New claims 12-20 recite subject matter that was removed from claims 1 and 4-10. Applicants note that the Patent Office's 35 U.S.C. §112, second paragraph, rejections of claims 6-10 have been addressed in new claims 16-20, which correspond to cancelled claims 6-10.

Support for new claims 12-20 is found in original claims 1 and 6-10, since new claims 12-20 capture material removed from claims 1 and 4-10. Additional support for claim 17 is found in the specification on page 10, lines 31-32. Additional support for claim 20 is found in the specification on page 9, line 34 through page 10, line 2. New claims 12-20 do not recite any new matter.

Applicants submit that new claims 12-20 are in condition for allowance and respectfully solicit the same.

VI. Conclusion

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

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Six dependent claims have been cancelled. Two independent claims have been added. Six dependent claims have been added. A check for \$168.00 is enclosed to cover the fees for the additional independent claims.

Respectfully submitted,

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Date: November 11, 2002

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